associated with said autoimmune disease comprising orally or enterally administering to said human at least one [member] antigen selected from the group consisting of autoantigens specific for said autoimmune disease, and autoimmune response-suppressive fragments of said autoantigens, in an amount effective to [treat] suppress an autoimmune response associated with said autoimmune disease, said suppression comprising elicitation of suppressor T cells specific to said administered antigen.

REMARKS

Reconsideration of this application is respectfully requested.

PENDING CLAIMS

Following entry of this Amendment, claims 1, 2, 9, 11-13, 15-18, and 20 will be pending. Claims 1 and 20 have been amended.

RELATED APPLICATIONS

Applicants hereby disclose several related applications. Many of these applications were filed immediately prior to the June 8, 1995 deadline related to GATT. A Form 1449 listing the applications is included with this response.

I. 08/105,912, filed 08/10/93, directed to treatment of multiple sclerosis by oral administration of myelin (Applicants' docket number 16104US3).

II. The following are Rule 60 divisional applications of the present application:

A. **08/454,580**, filed 05/30/95, directed to treatment of myasthenia gravis (Applicants' docket number 16104US7).

B. **08/454,581**, filed 05/30/95, directed to treatment of systemic lupus erythematosus (Applicants' docket number 16104US8).

C. **08/454,579**, filed 05/30/95, directed to treatment of autoimmune hemolytic anemia (Applicants' docket number 16104US9).

D. **08/455,072**, filed 05/31/95, directed to treatment of autoimmune thyroiditis (Applicants' docket number 16104USB).

III. The following is a Rule 60 continuation of the present application:

08/454,832, filed 05/31/95, directed to treatment of multiple sclerosis with analogs of MBP (Applicants' docket number 16104USC).

IV. 08/328,562, filed 10/24/94, directed to treatment of multiple sclerosis by administration of an autoantigen or its fragments (Applicants' docket number 16104US5). This application contains no claims specifically reciting administration of MBP.

V. The following are Rule 60 continuation applications of serial no. 08/328,562, listed above:

A. **08/463,946**, filed June 5, 1995, directed to treatment of autoimmune arthritis with collagen fragments or analogs (Applicants' docket number 16104USD).

B. **08/461,586**, filed 06/02/95, directed to treatment of autoimmune arthritis with type I or type III collagen (Applicants' docket number 16104USE).

VI. The following applications relate to peptides that contain immunodominant epitopes of MBP or a related T cell receptor:

A. **08/468,540**, filed 06/06/95, directed to specified peptides of MBP (Applicants' docket number 17644US1).

B. **08/469,640**, filed 06/06/95, a divisional application based on 08/046,354 directed to a method for suppressing immune function of $CD4^+$ T cells by administering, intravenously, a peptide comprising an immunodominant epitope of myelin basic protein (Applicants' docket number 17644US2).

C. **08/469,648**, filed 06/06/95, directed to peptides containing immunodominant epitopes of MBP (Applicants docket number 17644US3).

D. **08/297,395**, filed 08/11/94, directed to peptides having an immunodominant epitope region of human myelin basic protein (HMBP) (Applicants' docket number 05723US3).

E. **08/480,136**, directed to peptides containing a portion of a T cell receptor for an antigen that activates immune response against myelin

basic protein (Applicants' docket number 17644US4).

VII. The following application is a divisional application of **08/105,912**, listed above: **08/455,937**, filed 5/31/95, relating to a pharmaceutical dosage form containing bovine myelin for treatment of multiple sclerosis (Applicants' docket no. 16104US6).

VIII. The following applications relate to treatment of cell mediated autoimmune diseases by inhalation, aerosol, or nasal administration:

A. **08/419,502**, filed 04/10/95, directed to treatment of cell mediated autoimmune diseases by administering autoantigens in aerosol form (Applicants' docket no. 05432US2). This application includes claims specific to aerosol administration of myelin basic protein.

B. **08/480,151**, filed 06/07/95, related to prevention of cell mediated autoimmune diseases by inhalation of autoantigens, or fragments thereof (Applicants' docket no. 15432US3). This application includes claims specific to prevention of multiple sclerosis by inhalation of myelin basic protein.

C. **08/480,188**, filed 06/07/95, directed to treatment of cell mediated autoimmune diseases by administering autoantigens by inhalation (Applicants' docket no. 15432US4). This application includes claims specific to treatment of multiple scl rosis by inhalation of myelin

basic protein.

D. **08/465,815** filed 06/06/95, directed to treatment or prevention of cell mediated autoimmune diseases by nasally administering autoantigens (Applicants' docket no. 15432US5). This application includes claims specific to treatment or prevention of multiple sclerosis by nasal administration of myelin basic protein.

E. **08/465,816** filed 06/06/95, is a divisional application based on 08/419,502, directed to treatment of rheumatoid arthritis by administering autoantigens, or fragments of autoantigens, by inhalation in aerosol form (Applicants' docket no. 15432US6).

IX. **08/472,017** (applicants' docket number 06959US6) relates to "Bystander Suppression". This application describes administration of myelin basic protein, but contains no claims specific to that protein. Following are applications that are Rule 60 continuations of serial no. **07/843,752**, the parent application to **08/472,017**:

A. **08/461,591** filed June 5, 1995, directed to treatment of type I diabetes with gamma amino decarboxylase (Applicants' docket number 16959US2).

B. **08/468,996** filed June 6, 1995, directed to treatment of type I diabetes with glucagon (Applicants' docket number 16959US3).

C. **08/469,492** filed June 6, 1995, directed to treatment of autoimmune diseases by administering bystander antigens by nose or mouth (Applicants' docket number 16959US4). This application contains no claims specifically directed to myelin basic protein.

D. **08/461,662** filed June 5, 1995, directed to treatment of autoimmune diseases by administering bystander antigens by inhalation (Applicants' docket number 16959US5). This application contains no claims specific for myelin basic protein.

OBJECTION TO DISCLOSURE

The Examiner has objected to the disclosure, requesting that the term "MPB" be expanded. "MPB" is an error. It should read --MBP--, i.e., the abbreviation that is used throughout the rest of the specification. The specification has been amended herein, to correct this obvious error.

The Examiner states that claim 20 should indicate that it is only once amended, not twice amended as was erroneously indicated in applicant's prior Amendment. Applicants have amended claim 20 herein, and indicated that it is now twice amended.

Withdrawal of the objection to applicants' disclosure is respectfully requested.

OBJECTION AND REJECTION UNDER 35 U.S.C. §112, FIRST PARAGRAPH

The specification stands objected to, and claims 1, 2, 11-13, 15-18 and 20 rejected, under 35 U.S.C. §112, first paragraph. The Examiner has withdrawn the part of this rejection that was previously made under §101. The grounds for rejection remain the same, but are now made only under §112. The Examiner states that the showing of utility is not commensurate with the claims. While the Examiner accepts that the declaration of Howard Weiner is encouraging concerning the efficacy of orally administering MBP to treat multiple sclerosis, he states that there does not appear to be "sufficient factual support for the utility" in treating the diseases recited in claim 2. Applicants respectfully traverse this rejection.

This rejection is explicitly made on the basis of lack of "utility" under §112, and therefore clearly comes within the Commissioner's recent Guidelines concerning the utility requirement. Under those Guidelines, as well as under the applicable case law, the initial burden is on the Examiner to show why applicants' assertion that their invention functions as stated is not correct. There is no burden on applicants to supply factual support of any utility unless the Examiner has made such a showing.

It is respectfully submitted that no reasons have been made of record for demanding factual support for the utility of applicants' invention in treating the diseases encompassed by claim 1, i.e., T cell mediated or T cell dependent

autoimmune diseases. The outstanding Action refers to the reasons stated in paper no. 24 in support of the rejection for lack of utility. The rejections under §101 and §112 in paper no. 24, however, do not provide any such support. That paper questions whether one of ordinary skill could determine an effective dosage for treating the diseases encompassed. There have been, however, no reasons provided why the oral tolerance treatment that has been demonstrated for multiple sclerosis would not treat, e.g., the autoimmune diseases of claim 2 that the Examiner has required further factual showings for.

In addition, however, applicants, have in fact provided further factual showings demonstrating positive results in treating diseases encompassed by the claims (including claim 2), and what is submitted to be an exceptional amount of evidence of clinical results in humans. It is, according to Commissioner's Guidelines, the Solicitor's Office, and the Biotechnology Practice Specialist, only a rare situation which calls for submission of any data in humans. Further, the Commissioner's office has told BIO (the Biotechnology Industry Organization) that requests for human clinical data are only appropriate when a "cure" is claimed. Thus, while Applicants have previously submitted results showing encouraging results in humans in treatment of multiple sclerosis by the method of the present invention, this should not have been required.

Applicants have submitted clinical results for treatment of uveoretinitis

with S-antigen and treatment of rheumatoid arthritis with type II collagen, two other treatments within the scope of claim 1. Submission of three clinical trial results, i.e., involving three distinct diseases and three autoantigens within the scope of the claims, is submitted to be quite exceptional.

Following is a summary of the clinical evidence[1]:

- Dr. Weiner's declaration mailed 5/10/93 contains an exhibit describing clinical results in 10 patients administered type II collagen to treat rheumatoid arthritis according to the invention. Six out of ten of the patients received a considerable benefit as measured by reduction or elimination of most clinical symptoms and discontinuation or decrease of other drugs or several months following treatment. (Paragraph 8.)

- Dr. Weiner's declaration mailed 5/10/93 also describes clinical evidence of successful treatment of uveoretinitis with S-antigen according to the present invention. S-antigen was administered (orally) to two uveoretinitis patients, one of whom exhibited considerable improvement. (Paragraph 9.)

- The Examiner has not questioned the utility of applicants' embodiment of this invention for treating multiple sclerosis. Nevertheless, applicants note that in addition to the clinical results that have already been submitted in this

[1]Applicants note that treatments within claim 1 that are patentably distinct from the present claims and disclosure are appropriate evidence of utility.

application, a full-scale double-blind multicenter clinical trial concerning this treatment is now in progress. It is being conducted in 14 clinical centers in the United States and Canada, has enrolled more than 500 multiple sclerosis patents, and is expected to conclude in mid- to late-1997.

Thus, applicants' treatment of various autoimmune diseases with oral tolerance has been the subject of several separate human clinical studies involving three diseases: uveoretinitis by oral administration of the autoantigen S-antigen; rheumatoid arthritis by oral administration of the autoantigen type II collagen; and two clinical studies involving treatment of MS by oral administration of MBP.

It is submitted that the present record, containing clinical evidence of successful use of applicants' invention to treat at least three distinct autoimmune conditions with at least three autoantigens, is more than sufficient to support the breadth of claim 1 (and the depending claims). It is submitted that the Office should not fairly require more support than this.[2]

In the absence of sufficient reasons why these three successful uses are

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[2]Applicants have submitted evidence of a fourth clinical trial concerning treatment of type I diabetes with oral insulin. While this additional trial supports applicants' asserted utility, applicants wish to point out that at the time the present application was filed insulin was not recognized as an autoantigen in type I diabetes. Data from a fourth disease should, in any event, not be required since applicants have already demonstrated that their invention has broad utility, as stated in the specification.

not indicative of utility of the invention for the scope of the autoimmune conditions and autoantigens encompassed by the claims, it is respectfully submitted that the outstanding rejection for lack of utility under §112, first paragraph is improper and should be withdrawn.

The prior Examiner raised the issue of whether applicants' specification enabled one to treat humans with MBP, noting that the specification disclosed experiments in rats using small dosages (e.g. 25 μg, 100 μg, 500 μg) while humans were administered much larger dosages in the trial described in Dr. Weiner's previous declaration. Specifically, the prior Examiner stated that the dosage used in the MS trial of 300 mg was different from the dosage used in rats, and that, in view of unpredictability in the art, the "protocol" in the specification could not be "translated" into effective "parameters" for treating humans.

It is not entirely clear to applicants whether this basis of rejection has been maintained by the present Examiner. In any event, Applicants respectfully disagree with the prior Examiner's assertion and submit that the facts of record establish that one skilled in this art could treat humans suffering from multiple sclerosis with effective dosages of MBP (and could treat other autoimmune conditions with other autoantigens encompassed by the claims).

That smaller doses of MBP were administered to rats than to humans does not appear to be appropriate evidence of non-enablement. Normally, humans are

administered larger effective doses than rats for any given therapeutic agent.

Further, the fact that applicants were able to establish an effective dosage for treating multiple sclerosis is unrebutted factual evidence that those of ordinary skill in this art could do so. No reasons have been provided why undue experimentation was required in the clinical studies of record in which an effective dosage was administered.

Also, at page 8, lines 14-17, applicants' specification teaches that the autoantigen of the invention is generally administered in an amount of from 1 to 1000 mg per day, preferably 25 to 850 mg per day. Thus, 300 mg/day, the amount that the prior Examiner concluded was not enabled, is right in the middle of the preferred range disclosed by applicants' specification. This alone is respectfully submitted to be clear evidence that applicants' specification enables an effective dosage to be administered.

Even for a dosage outside of the general range stated in the specification, there are no reasons of record why one skilled in this art could not determine, through extrapolation from animal data, or from conventional dosing studies, what an effective amount would be.

The prior Examiner questioned whether extrapolating dosages from experimental data in animals to dosages in humans required undue experimentation. It is not clear what part of this determination the prior Examiner believed could be

unduly difficult. Extrapolation of rat dosages to human dosages for autoimmune conditions, however, is submitted to be well within ordinary skill in the art. The enclosed article by Trentham et al. (concerning one of the successful collagen trials described above) states that the dose used "was extrapolated from experiments in the rat adjuvant arthritis model". Similarly, the human doses used in the present multicenter trial were extrapolated from the rodent data. It should also be noted that treatment of EAE in rodents is disclosed in the present specification as being achieved using dosages of MBP within a relatively wide dosage range (25 - 500 micrograms; Example 1, Table I, spec. p.16). Certainly this does not provide a basis for doubting the efficacy of amounts within the disclosed human dosage range.

In any event, the fact that dosages have been determined to administer to humans for three embodiments of the invention (as discussed above) is submitted to be strong evidence that one skilled in the art can determine such dosages in view of applicants' specification and general knowledge.

For these reasons, applicants request that the Examiner withdraw the objection to the specification and the rejection of claims 1, 2, 11-13, 15-18 and 20 under 35 U.S.C. §112, first paragraph.

REJECTION UNDER 35 U.S.C. §103

Claims 1, 2, 9, 11-13, 15-18 and 20 stand rejected under 35 U.S.C. §103 as obvious over Campbell *et al.* in view of Whitacre *et al.* and/or Nagler-

Anderson *et al.*

The prior Actions state that Campbell teaches administering MBP parenterally to patients suffering from multiple sclerosis, Whitacre discloses orally administering MBP to prevent EAE in rats, and Nagler-Anderson teaches intragastrically administering collagen type II to prevent collagen induced arthritis in rats. Therefore, the Examiner reasons, it would have been obvious to treat multiple sclerosis by orally administering MBP. In view of the amendments to the claims and the discussion below, applicants respectfully traverse this rejection.

Independent claims 1 and 20 have been amended herein to recite that the claimed method relates to treatment of a human "exhibiting an autoimmune response associated with said autoimmune disease." This clarifies that applicants' invention relates to administration to humans after they have developed an autoimmune response that is associated with the T cell-mediated or dependent autoimmune disease being treated.

Claims 1 and 20 have also been amended to recite that the claimed method relates to "suppression comprising elicitation of suppressor T cells specific to said administered antigen" and that the antigen is administered (in an amount that is effective to) "suppress said autoimmune response associated with said autoimmune disease." Support for these amendments can be found, for example, at page 8, paragraphs 1 and 2. These amendments clarify that the method of applicants'

invention involve eliciting suppressor T cells that suppress an autoimmune condition associated with the T cell-mediated or dependent autoimmune disease being treated.

As discussed previously by applicants, the Whitacre Abstract describes an attempt to prevent onset of EAE by an anergy mechanism (termed "antigen-specific unresponsiveness"). The Whitacre Abstract, however, teaches against active suppression by oral administration of MBP. Specifically, the Abstract states that "LNC or spleen cells from MBP-fed rats were unable to transfer EAE." Applicants, on the other hand, teach in their specification that such "adoptive transfer" did occur in their experiments. In other words, applicants teach that they elicited suppressor T-cells that suppressed an autoimmune response associated with EAE. Whitacre et al. teach that they did not. It appears that applicants were probably successful in this, while Whitacre et al. were not, because applicants administered unprotected MBP while Whitacre administered a protected form of MBP (protected with "STN"). (This aspect of the Whitacre experiments was later more fully described in Bitar et al., of record.)

The prior Examiner disagreed that Whitacre et al.'s failure to achieve "active suppression" was relevant because applicants' claims did not recite active T cell suppression (Paper No. 24). As noted above, applicants have amended their claims to recite that suppression of the autoimmune response associated with the autoimmune disease comprises "elicitation of suppressor T cells specific to said administered antigen" (i.e., active suppression). As amended, these claims are

submitted to be clearly distinguished from the teachings of Whitacre et al.

Applicants also note that a treatment based on anergy, i.e., Whitacre et al.'s treatment, could not have been reasonably predicted to work in humans: anergy is successful only against activated T cells that recognize the very same antigen administered. If the human autoantigen were unknown (as was the case in 1987), or if it varied from patient to patient (a likely possibility in outbred human beings) no reasonable expectation of success could attach to the oral tolerization treatment. It was the present inventors who demonstrated that oral tolerization can be adoptively transferred, thus raising the expectation that orally administering MBP would be effective in humans suffering from multiple sclerosis. Specifically, prior to applicants' invention, there was no expectation that immune events (elicitation of suppressor T cells) common to rodents with healthy immune systems assaulted with a single known disease inducing antigen and to humans afflicted with an immune disorder of unknown etiology would induce tolerance.

In addition, the present specification describes experiments demonstrating suppression of disease after induction of an autoimmune response associated with autoimmune disease. The present claims have been amended herein to recite treatment of a human "exhibiting an autoimmune response associated with said autoimmune disease", i.e., after an autoimmune response is established. Whitacre, on the other hand, only discloses experiments in which MBP was

administered to rats before an autoimmune response was induced (i.e., before EAE was induced). It provides no reasonable expectation of success in suppressing disease by administering an autoantigen after an autoimmune response associated with the autoimmune disease is exhibited.

Instead, the cited art shows there was no such expectation. Nagler-Anderson et al. teach that oral ("intragastric") administration of an autoantigen to an animal already exhibiting an autoimmune response did not work, stating:

> In the present studies . . . eight intragastric administrations of type II collagen given between days 10 and 29 after immunization with type II collagen in complete Freund's adjuvant did not result in decreased incidence or severity of CIA. (page 7445, col. 2)

Thus, the Nagler-Anderson reference shows there was no reasonable expectation of success with respect to either applicants' generic claims, or claims specifically directed to MS, and in fact teaches away from the present invention. In other words, the Nagler-Anderson reference appears to teach against treating a human already exhibiting an autoimmune response associated an autoimmune disease, as claimed. (Nor does Nagler-Anderson disclose or suggest elicitation of suppressor T cells to suppress an autoimmune response associated with the autoimmune disease, as claimed.)

Campbell et al., the primary reference cited, is respectfully submitted to be further removed from the present invention than the secondary references. The

Campbell reference only describes intravenous administration of MBP. The route of administration of an antigen, however, is well known to be a crucial parameter in determining the immune response that will result. Therefore, one skilled in this art could not have had any reasonable expectation of success of oral administration in humans based on Campbell's experiments involving intravenous administration in humans. For example, as stated by Wood *et al.*, *Transplantation*, 1985, 39:56 "the route used for immunization [meaning antigen administration] is of critical importance" for the suppressive effect of antigens. (See page 60, col. 2, last paragraph.) Wood *et al.* describe experiments showing that only intravenous injection of purified erythrocytes from donor rats inhibited allograft rejection in rats. Subcutaneous and intraperitoneal injections failed to suppress rejection. (In other words, only the intravenous route was effective, and every other route attempted produced results that were the same as those observed in control rats.)

Furthermore, the Campbell reference provides no reason to predict any success in suppressing an autoimmune response associated with MS by eliciting suppressor T cells specific to the orally administered antigen, as now claimed.

For these reasons alone, it is submitted that the outstanding rejection under 35 U.S.C. §103 should be withdrawn.

For the additional reasons stated below, however, applicants submit that there was no such reasonable expectation of success that a T cell mediated, or T cell

dependent autoimmune disease could be successfully treated by oral administration of an autoantigen.

In 1986/1987, those skilled in the fields of neuroimmunology and autoimmune diseases believed that there was a strong possibility that oral administration of myelin basic protein (MBP) to an individual afflicted with multiple sclerosis could worsen the patient's condition. This was believed to be a significant possibility because it was thought that individuals afflicted with multiple sclerosis may already have been sensitized to the autoantigen responsible for the disease. Although it was not known for certain that MBP was the autoantigen responsible for MS, this was suspected to be the case. Those skilled in this field did not, however, turn to MBP as a treatment option. On the contrary, it was feared that oral administration of MBP could result in a heightened autoimmune reaction that would be seriously detrimental. There was no expectation that MBP would work to alleviate MS in humans, despite reported animal experiments, such as those of Whitacre.

In the mid-1980s, those in this field discussed the possible use of oral tolerization in other neuroimmunologic disorders including multiple sclerosis and polyneuritis. The various putative antigens, including myelin basic protein and other molecules, were not used because of fear that such treatment would worsen the diseases in question. The work with animal models, such as the brief report by Whitacre et al., did not encourage those in the field to apply oral tolerance to humans

as a way to treat autoimmune diseases.

In 1986 or 1987, it was known that patients afflicted with multiple sclerosis have defects in their ability to generate immune suppression. Thus, even if an autoantigen were orally administered to such patients, the autoantigen might not have triggered the suppression response necessary to dampen the subject's autoimmune reaction. Because of this defect in suppression, such administration ran the risk of further sensitization, which would aggravate the patient's condition.

Therefore, the teachings in the Campbell, Whitacre and Nagler-Anderson references would not have led those skilled in the field of autoimmune disease to experiment with the use of myelin basic protein in the treatment of multiple sclerosis because of the fear of worsening the disease, as discussed above. In fact, as noted above, Nagler-Anderson, which discloses that oral administration of collagen was ineffective after induction of autoimmune response associated with collagen induced arthritis, directly teaches away from the present invention.

In addition, however, there are significant differences between the animal model disclosed in Whitacre and human patients that are afflicted with autoimmune response associated with multiple sclerosis. In 1987, prior to the filing of the ancestor to the present application, the results in the EAE model could not have been relied on as demonstrating a reasonable expectation of success in humans. In the EAE model, laboratory rats are orally administered the same autoantigen that is used to

induce EAE. EAE is somewhat akin to MS, and is useful for research, but is not the same disease in the same host and was not expected to behave in the same way. Also, the EAE model is based on the prevention or suppression of an acute condition that is artificially induced. In other words, the animal is not suffering from a chronic disease, has not been sensitized prior to administration of the autoantigen, and does not have an abnormal, compromised, or suppressed immune system associated with chronic autoimmune disease even before manifestation of clinical symptoms. This is quite different from a human patient afflicted with a chronic autoimmune condition such as multiple sclerosis. The patient has been sensitized to an autoantigen over a long period of time and is afflicted with a chronic condition which is not reversible, i.e, for which there is no effective treatment.

Nor does the animal model employed by Whitacre et al. and similar models employed prior to 1987 address concerns about immunosuppression and sensitivity in human patients suffering from a persistent chronic disease. The models are directed to an acute autoimmune episode induced in laboratory animals, where sensitivity and immunosuppression of the kind observed in humans does not arise. Thus, the animal model and animal results were not readily transferable to humans. Moreover, the animal model had no bearing on the real concern that oral administration of an autoantigen to humans (such as MBP for MS) would do more harm than good.

Therefore, the prevention of an artificially induced surrogate disease in Lewis rats (EAE) that is described in Whitacre was not readily transferable to the treatment of a chronic and therapy resistant disease in humans (MS). There was no reasonable expectation that oral administration of MBP could be successfully used to treat MS in humans.

The Whitacre Abstract states that the results described "suggest that oral administration of MBP induces a state of antigen-specific unresponsiveness, which could be of value in establishing therapeutic protocols or multiple sclerosis." For the reasons described above, this was not an indication to skilled practitioners that oral feeding of MBP could be successfully applied to humans afflicted with MS. Also, the autoantigen for MS was not known. While MBP was a known autoantigen for EAE in rats, it was a suspected autoantigen in human MS. Since the autoantigen for MS was unknown, a person of ordinary skill in the field would not have understood the Whitacre Abstract as any indication of a successful human therapy. The quoted sentence from the Whitacre reference is at best an invitation to experiment (i.e., an improper basis for an obviousness rejection). Discussion of future avenues for research are routine in abstracts of this kind, as is the hope that animal data might lead to more fruitful research in humans. The successful application of MBP to MS patients according to the application, and as demonstrated by clinical studies was not predictable with any reasonable expectation of success.

For these reasons, applicants request that the rejection of claims 1, 2, 9, 11-13, 15-18 and 20 under 35 U.S.C. §103 as obvious over Campbell *et al.* in view of Whitacre *et al.* and/or Nagler-Anderson *et al.* be withdrawn.

OBVIOUSNESS-TYPE PATENTING

The Examiner withdrew the rejection for obviousness-type double patenting over application serial no. 07/596,936 since that application has been abandoned, but requested information on related applications. The related applications are described above.

CONCLUSION

Particularly in view of the very long time that this case has been pending, applicants submit that the present claims are now in condition for allowance. Issuance of a notice to that effect is earnestly solicited.

Respectfully submitted,

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Enclosures: Trentham et al.
Wood et al.